REMARKS

Claims 6, 7, 20, 24 and 27 are active. Claim 24 is directed to the elected species where component (B) is zingerol and has been indicated as being allowable. The claims have been revised for clarity. Accordingly, the Applicants do not believe that any new matter has been added. Favorable consideration and allowance of this application is now respectfully requested.

Election/Restriction

The Applicants previously elected Group II (method of treatment) and the a species of compound for use in the elected method comprising (A) chlorogenic acid and (B) a central nervous system stimulating component. On June 2, 2005 the Applicants were required to further elect a single species of component (B) and subsequently elected (B) zingerol which is a heat component of ginger (*Zingiberaceae*). The claims as directed to the elected species (A) chlorogenic acid + (B) zingerol have been found in condition for allowance except for formal matters. The Applicants respectfully request that the other specific heat components of ginger (e.g., zingerone, shogaol, etc.) recited in the claims also be examined, since the previously elected zingerol falls within the subgenus of heat components from ginger.

Examination has now been directed to a species selected by the Examiner: (A) chlorogenic acid + (B) capsaicin (a heat component from red pepper, *Capsicum*). The Restriction Requirement has been made FINAL.

Rejection—35 U.S.C. § 112, second paragraph

Claims 6, 7, and 20 were rejected under 35 U.S.C. 112, second paragraph, as indefinite for employing the term "heat component". This term is well-know to the public and within the food and pharmaceutical sciences. In fact, the Scoville scale was developed in

1912 to measure the hotness of foods such as peppers containing capsaicin (see attached Wikipedia article "Scoville scale"). Moreover, heat components are both described and exemplified on page 8 of the specification. Therefore, the Applicants request that this rejection be withdrawn since one of skill in the art would understand the meaning of this term when read in light of the specification.

Rejection—35 U.S.C. § 103

Claims 6, 7, 20 and 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., Chinese Pharm. Journal 46:575 and Hsia et al., U.S. Patent No. 6,440,464. These teachings in these documents do not make the current invention obvious, since they provide no suggestion or motivation to combine isolated chlorogenic acid and capsaicin.

Cheng, Table 1 on page 579, only refers to the effects of chlorogenic acid and does not disclose or suggest combining it with capsaicin.

Hsia et al., U.S. Patent 6,440,464, discloses a complex mixture of ingredients, including capsaicin. However, it does not disclose the combination of isolated chlorogenic acid and capsaicin, nor provide any motivation for combining chlorogenic acid and capsaicin, or for using this combination to treat hypertension.

The Official Action cites col. 1, lines 16-22, of this patent as suggesting that capsaicin has an antihypertensive effect. However, this section of Hsia refers to a complex composition including many other ingredients besides capsaicin, including fish oil, garlic and vitamins. Importantly, Hsia, col. 3, lines 33-37, specifically points out that the novelty of the Hsia composition lies in this complex combination of ingredients.

Moreover, while Hsia, col. 4, lines 1-3, indicates an object of the invention is to provide compositions that will lower blood pressure, there are no examples of the claimed composition actually reducing blood pressure. Thus, the Hsia patent merely alleges that the

claimed composition treats cardiovascular disease, but provides no evidence that it does. So far as treatment of hypertension is concerned, Hsia is a non-enabling reference.

Furthermore, Hsia attributes no anti-hypertensive properties to capsaicin, one of the ingredients of the complex Hsia composition. Rather, col. 2, lines 59-col. 3, line 2 only describe antimicrobial and analgesic properties of capsaicin. As far as Hsia is concerned capsaicin has no anti-hypertensive effects. Therefore, neither Cheng nor Hsia provide any suggestion to specifically combine isolated chlorogenic acid and capsaicin.

Even were there some general motivation to treat hypertension by combining the products of Cheng and Hsia, these documents provide no reasonable expectation of success that this combination would actually treat hypertension. The prior art does not suggest that the combination of chlorogenic acid and a heat component, such as zingerol or capsaicin, would be effective for treating hypertension. On the other hand, Example 2 of the specification does show the anti-hypertensive activity of such a combination.

Moreover, one with ordinary skill in the art would not reasonably expect that a complex mixture of ingredients of Hsia and chlorogenic acid would necessarily exhibit any effect on hypertension since the interaction of the Hsia composition and chlorogenic acid could negate or inhibit the effects of chlorogenic acid as shown by Cheng. Common drug interactions include pharmacodynamic (where one drug competes for the same receptor site as another) and pharmacokinetic (where the absorbtion, distribution, metabolism or excretion of one drug is affected by the presence of another). For example, it is commonly known that consumption of grapefruit juice inhibits the uptake or activity of many drugs (see Oesterheld, attached). Hsia, in fact, indicates that grapefruit juice (col. 7, lines 37-43), as well as other complex and potentially suspect juices and herbal components are integral components of his mixture. Due to complexity of the mixture of Hsia and the possibility of drug interactions which negate the hypertensive effects of chlorogenic acid of Cheng (or alternatively, those of

the Hsia composition) one with ordinary skill in the art would not have had a reasonable expectation of success in treating hypertension by merely combining the products of Cheng and Hsia.

Since neither Cheng nor Hsia suggest the specific combination of the present invention, nor provide any reasonable expectation of success for using this combination to treat hypertension, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—Obviousness-type Double Patenting

Claims 6, 7, 20 and 27 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over Claim 5 of U.S. Patent No. 6,458,392, in view of U.S. Patent No. 6,440,464. This rejection is traversed since Claim 5 of the '392 patent requires administering a soy sauce containing a coffee bean extract. However, the present claims require isolated chlorogenic acid as well as an isolated heat component, such as zingerol or capsaicin. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Provisional Rejection—Obviousness-type Double Patenting

Claims 6, 7, 20 and 27 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending U.S. Applications 09/922,694, 10/826,289, 10/632,810, 10/810,611, or 11/106,428, in view of U.S. Patent No. 6,440,464. The Applicants respectfully request that these provisional rejections be held in abeyance pending the identification of otherwise allowable subject matter in the present application, see MPEP 804(I)(B).

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

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Scoville scale

From Wikipedia, the free encyclopedia.

The **Scoville scale** is a measure of the *hotness* of a chile pepper. These fruits of the Capsicum genus contain capsaicin, a chemical compound which stimulates heat-receptor nerve endings in the tongue, and the number of Scoville heat units (SHU) indicates the amount of capsaicin present. Many hot sauces use their Scoville rating in advertising as a selling point.

It is named after Wilbur Scoville, who developed the **Scoville Organoleptic Test** in 1912. As originally devised, a solution of the pepper extract is diluted in sugar water until the 'heat' is no longer detectable to a panel of (usually five) tasters; the degree of dilution gives its measure on the Scoville scale. Thus a sweet pepper, containing no capsaicin at all, has a Scoville rating of zero, meaning no heat detectable even undiluted. Conversely, the hottest chiles, such as habaneros, have a rating of 300,000 or more, indicating that their extract has to be diluted 300,000-fold before the capsaicin present is undetectable. 15 Scoville units is equivalent to one part capsaicin per million. The greatest weakness of the Scoville Organoleptic Test is its imprecision, because it relies on human subjectivity.

Later analytical developments such as high performance liquid chromatography (HPLC) (also known as the "Gillett Method") have now enabled the Scoville rating to be determined by direct measurement of capsaicin rather than sensory methods.

List of Scoville ratings

Scoville ratings may vary considerably within a species—easily by a factor of 10 or more—depending on seed lineage, climate and even soil. This is especially true of habaneros.

16,000,000	Pure capsaicin, dihydrocapsaicin
9,100,000	Nordihydrocapsaicin
8,600,000	Homodihydrocapsaicin and homocapsaicin
5,300,000	Police grade pepper spray
2,000,000	Common pepper spray
855,000	Naga Jolokia pepper (validity is disputed)
560,000 - 890,000	Thai Green Chilies
350,000 - 580,000	Red Savina habanero
100,000 - 350,000	Habanero chile
100,000 - 325,000	Scotch bonnet
100,000 - 225,000	African birdseye (aka "African Devil")
100,000 - 200,000	Jamaican hot pepper
100,000 - 125,000	Carolina cayenne pepper
95,000 - 110,000	Bahamian pepper
85,000 - 115,000	Tabiche pepper
50,000 - 100,000	Chiltepin pepper
50,000 - 100,000	Rocoto
40,000 - 58,000	Pequin pepper
40,000 - 50,000	Super chile pepper
40,000 - 50,000	Santaka pepper
30,000 - 50,000	Cayenne pepper
30,000 - 50,000	Tabasco pepper
15,000 - 30,000	de Arbol pepper

12,000 - 30,000 Manzano pepper, Ají
5,000 - 23,000 Serrano pepper
5,000 - 10,000 Hot wax pepper
5,000 - 10,000 Chipotle
2,500 - 8,000 Jalapeño
2,500 - 8,000 Santaka pepper
2,500 - 5,000 Guajilla pepper
1,500 - 2,500 Rocotilla pepper
1,000 - 2,000 Pasilla pepper
1,000 - 2,000 Ancho pepper
1,000 - 2,000 Poblano pepper
700 - 1,000 Coronado pepper
500 - 2,500 Anaheim pepper
500 - 1,000 New Mexico pepper
500 - 700 Santa Fe Grande pepper
100 - 500 Pepperoncini pepper
100 - 500 Pimento
0 Sweet bell pepper

Further reading

- The Journal of the American Pharmacists Association 1912; 1:453-4

External links

- Hottest Hot Sauces & Scoville Ratings (http://www.sweatnspice.com/hottest_sauces.php)
- Pepper Facts (http://www.thescarms.com/hotstuff/pepperfacts.htm)
- Record for Red Savinas (http://www.guinnessworldrecords.com/index.asp?id=49118)

Retrieved from "http://en.wikipedia.org/wiki/Scoville_scale"

Categories: Scales | Peppers

Grapefruit Juice and Drug Interactions

Jessica R. Oesterheld, M.D.

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In an interaction study of felodipine and ethanol in which grapefruit juice (gfj) was added to ethanol to mask the taste, it was serendipitously found that gfj augmented felodipine's bioavailibility (Bailey 1989). The list of drugs, low clearance CYP3A substrates, demonstrated to be significantly effected by gfj tops 40 and is growing (see below). Psychiatrists should note that triazolam (Hukkinen 1995), midazolam (Kupferschmidt 1995), clomipramine (Oesterheld 1997), buspirone (Lilja 1998), carbamazepine (Garg 1998), diazepam (Ozdemir 1998) and others are listed.

Although CYP 3A4, CYP 3A5, CYP 1A1 and CYP 2D6 are present in the enterocytes that line the lumen of the gut as well as the liver, CYP3A4 is by far the most abundant in both areas (Lown 1997). There are large variations in the amount of CYP present in gut or liver between individuals, and individuals also have differing amounts of CYP3A4 present in the gut and in the liver. Gfj is a competitive and mechanism-based inhibitor, (similar in potency to TAO) of intestinal CYP 3A4 and CYP 3A5 when a single glasses of gfj are consumed (Veronase 2003) and also of liver CYPs (when triple that dose is ingested (Veronase 2003). Inhibition occurs almost immediately if the gfj dose is high enough (e.g., a single glass of reconstituted frozen concentrate inhibits CYP3A4 within the first 4 hours. Schmiedlin-Ren 1997). Drug inhibition can last up to 3 days after gfj intake ceases (Tankanaga 2000a, Tankanga 2000 b).

Different preparations of gfj vary in their capacity to inhibit CYP3A. Reconstituted frozen concentrate is generally used in clinical studies, and it is a more potent CYP3A4 inhibitor than fresh gfj because gfj rind (which contains an oil that itself is a potent CYP3A inhibitor) is added to frozen concentrate during processing (Schmiedlin-Ben 1997). White gfj is a more potent inhibitor than pink gfj (Fukuda 2000). There are other fruits such as pomelos that are related to grapefruits that are also known to increase the concentration of CYP3A4 substrates (e.g., tacrolimus

Egashira 2003), and there is a possibility that grapefruit jams may also effect drugs. Fruits found in Japan (e.g., banpeiyu, hassaku, takaoka-buntan or Tamatama, Fujita 2003) have similar properties.

Although two components found in grapefruit juice (gfj), 6'7'hydroxybnergamottin (HBG) and 6-epoxyBG have been shown to be mechanism based inhibitors of intestinal CYP3A4 and CYP3A5 (Lown 1997, Schmiedlin-Ben 1997), other furanocoumarins in gfj have been also shown to have potent inhibitory effects on CYP3A4 (Guo 2000). HBG and naringen may be responsible for gfj's PGP inhibition (Ohnishi 2000, Eagling 1999). Gfj peel is often added to the juice during the manufacturing process and epoxybergamottin was identified as a potent CYP3A4 inhibitor and may be present in gfj (Wangensteen 2003). Recently components in orange juice, methoxyflavones have been shown to be PGP inhibitors in vitro (Tankanaga 2000). Bergamottin has been shown not to contribute to CYP inhibition (Baily 2003).

To be significantly effected by gfj, not only must a CYP3A substrate have low bioavailibility, but it must have a significant portion metabolized by intestinal CYP3A. Conversely, if a known substrate of CYP 3A can be shown be have no significant interaction with gfj (with single 8 ounce consumption), it can be assumed that it is mostly metabolized by hepatic CYPs or have a high bioavailibility (e.g., alprazolam PMID). The ability to analyze the relative contributions of liver CYP 3A metabolism and intestinal CYP 3A metabolism and to a CYP3A drug-drug interaction is now available by adding gfj as a "knock-out" drug to standard bioavailibility studies. (Hall 1999).

If a drug is known to be primarily either an inducer or inhibitor of intestinal CYP3A4 (e.g., modafinil as an inducer PMID 12537513) , then a clinician can predict that the drugs listed below will be effected. Conversely, if a drug is known to primarily effect hepatic CYP3A4, then one can predict that no interaction will occur. Naturally, some individuals may have a preponderance of one or the other CYP and will not follow this rule.

Gfj also has a demonstrated effect of intestinal transporters. Fexofenadine is not metabolized by CYPs, but it is handled by the influx transporter OATP (organic anion transporter polypeptide). If the two are coadministered, the Cmax of fexofenadine is reduced by 30% (Banfield 2002). The effects of gfj on P-gps are not

completely understood at this time, but it is believed that it does effect P-gp substrates with low bioavailability (Dresser 2003).

Intestinal CYP3A4 substrates: (PMID number given if not cited below in the reference list. Note some additions have been made from Medical Letter vol 46: issue 1173, 2004)
albendazole (Albenza) PMID 12139218
amiodarone (Cordarone)
artemether
astemizole
atorvastatin
budesonide (Entocort EC)
buspirone
carbamazepine (Tegretol)
celiprolol PMID 12621384
cervistatin
cisapride
clomipramine
cyclosporine
dextromethorphan PMID 12095536
diazepam
diltiazem (Cardizem) PMID 12451428
erythromycin
ethinyl estradiol
felodipine (Plendil)
halofantrine PMID 12426515
isradipine
LAAM
loratadine
losartan PMID 11477318
lovastatin
methadone
methylprednisolone (Medrol)
midazolam
nefazodone
nelfinavir
nifedipine
nicardipine (Cardene)
nimodipine
nisoldipine (Sular) Takanaga H et al Clin Pharmacol Ther 2000;67:201-214

praziquantel (Biltricide) PMID 11959616
quetiapine
quinidine
ritonavir
saquinavir
sertraline
sildenafil
simvastatin (Zocor)
tacrolimus (Prograf) PMID 12698101
terfenadine
trazodone
triazolam
verapamil (Calan)
zaleplon

Who drinks gfj anyway? The acuity to detect a bitter taste is genetically determined by sensitivity to 6-n-propylthiouracil.and may be negatively related to liking gfj (Dewnowski 1997). Gfj is not only consumed by choice by spoon or glass for breakfast, but it is inadvertently consumed via fruit combination drinks in which it is often used as a base. Just peruse the cans and bottles in the juice section of your supermarket to see how commonly it is listed as an ingredient. Another natural source of furanocoumarins can be found in herbal medicines and some are potent inhibitors of CYP3A4 (Guo 2000). This raises the possibility of additional herb-drug interactions.

There is another reason to limit gfj ingestion. In large epidemiological studies of both men and women, high GFJ intake has been associated with renal stones (Curhan GC. 1998, Curhan GC 1996). Causation may be indirect. One possibility is that GFJ contains a polyphenol that inhibits 11beta-hydroxysteroid dehydrogenase that enhances renal mineralocorticoid effects and leads to decreased serum potassium levels (Reidenberg 2000). It is known that high potassium intake is associated with lowered risk of renal stones (Hirvonen 1999). Another possibility is that naringens can bind calcium and create a calcium intense environment in the kidney (Ameer 1998).

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